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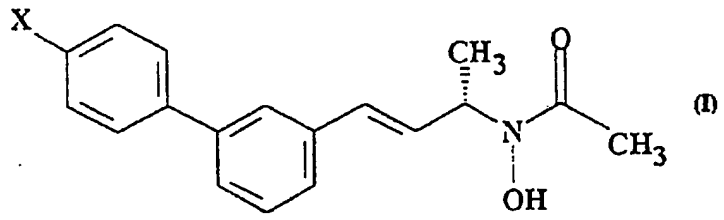
(54) Title: CYCLOOXYGENASE AND 5-LIPOXYGENASE INHIBITING N(3-BIPHENYLYL-1(S)-METHYL-2-PROPENYL) ACETOHYDROXAMIC ACID DERIVATIVES



(I)

(57) Abstract

The present invention is concerned with novel hydroxamic acid derivatives of formula (I) and their use in medical therapy, particularly in the prophylaxis or treatment of clinical conditions for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachidonic acid metabolic pathway is indicated. The invention also relates to pharmaceutical formulations and processes for the preparation of compounds according to the invention. In formula (I), X is cyano, fluoro, or chloro; or a salt, solvate, or physiologically functional derivative thereof.

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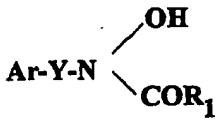
CYCLOOXYGENASE AND 5-LIPOXYGENASE INHIBITING N(3-biphenylyl-1(s)-methyl-2-propenyl) ACETOHYDROXAMIC ACID DERIVATIVES.

The present invention is concerned with hydroxamic acid derivatives which are inhibitors of the lipoxygenase and cyclooxygenase mediated arachidonic acid metabolic pathway, with processes for their preparation, with pharmaceutical formulations containing said derivatives and with their use in medicine.

European Patent Specification 0196184 describes hydroxamic acid derivatives having the ability to inhibit the enzymes 5-lipoxygenase and cyclooxygenase in the mammalian arachidonic acid cascade. The compounds in question include those of formula



wherein,

Y is C_{2-10} alkenylene;

R_1 is C_{1-4} alkyl, amino, C_{1-4} alkylamino, or di-C_{1-4} alkylamino;

and Ar is phenyl optionally substituted by one or more substituents independently selected from:

(i) C_{1-4} alkyl (which may itself be optionally substituted by one or more halogen atoms), C_{1-4} alkoxy, halo, nitro, amino, carboxy, C_{1-4} alkoxycarbonyl, and hydroxy;

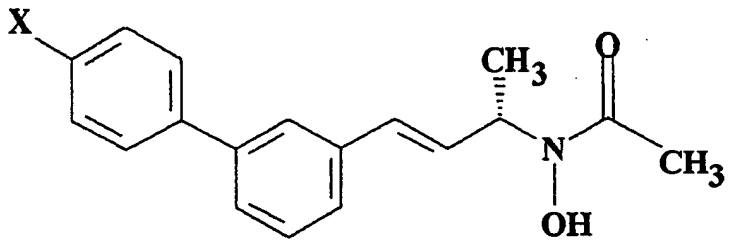
(ii) phenyl optionally substituted by one or more substituents independently selected from those specified in (i).

WO 90/12008, WO 92/10469, and WO 92/01682 also disclose compounds having lipoxygenase inhibitory activity.

We have now discovered a class of compounds related to those of EP0196184, WO 90/12008, WO 92/10469, and WO 92/01682 having exceptionally good

pharmacological and physical properties; particularly, with respect to their potent 5-lipoxygenase inhibitory activity, long duration of action and/or crystallinity.

According to the present invention, therefore, there is provided a compound of formula (I)



(I)

wherein X is cyano, fluoro, or chloro;

or a salt, solvate, or physiologically functional derivative thereof.

In the alternative, the present invention provides a compound selected from:

(E)-N-[3-(4'-Cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid;

(E)-N-[3-(4'-Fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid;

(E)-N-[3-(4'-Chloro-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid;

and salts, solvates and physiologically functional derivatives thereof.

Salts of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion is pharmaceutically acceptable. However, salts having non-pharmaceutically acceptable counterions are within the ambit of the present invention, either for use as intermediates in the preparation of compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

Salts according to the invention include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium, salts with organic bases such as dicyclohexylamine and N-methyl-D-glucamine, and salts with amino acids, such as arginine and lysine.

By the term physiologically functional derivatives is meant chemical derivatives of compounds of formula (I) which have the same physiological function as the free compound of formula (I), for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include compounds of formula (I) in which the hydroxyl of the hydroxamic acid functional group has been converted to a urethane, an alkyl ether, or an ester.

The definition of the compounds of the invention provides compounds of formula (I) in the (S) form. However, the present invention also provides compounds of formula (I) as mixtures of the (R) and (S) forms, provided that the (R) form constitutes less than 50% of the mixture.

As mentioned hereinbefore, compounds of formula (I) and salts, solvates, and physiologically functional derivatives thereof have use in the prophylaxis and treatment of clinical conditions for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachidonic acid metabolic pathway is indicated, as demonstrated hereinafter in the 5-lipoxygenase and cyclooxygenase inhibition assays in which representative compounds of the present invention have been shown to be active. For example, the ability of compounds of formula (I) to inhibit the lipoxygenase and cyclooxygenase mediated arachidonic acid metabolic pathways, renders them useful for the prophylaxis and treatment of spasmogenic conditions, allergic conditions, tumour formation, conditions involving blood platelet aggregation, and inflammatory conditions.

Examples of spasmogenic conditions are those involving smooth muscle tissue, especially airway smooth muscle constriction such as asthma (including idiopathic bronchial asthma), bronchitis and arterial smooth muscle constriction such as coronary spasm (including that associated with myocardial infarction, which may or may not lead to left ventricular failure resulting in cardiac asthma), ischemia-induced myocardial injury, and cerebral spasm or 'stroke' (which may lead to central nervous pathophysiology). Other examples include bowel disease caused by abnormal colonic muscular contraction such as the conditions known as 'irritable bowel syndrome', 'spastic colon' and 'mucous colitis'.

Examples of allergic conditions are extrinsic asthma, allergic skin diseases having a total or partial allergic origin, such as eczema, allergic bowel diseases (including coeliac disease), allergic eye conditions, such as hayfever (which may additionally or alternatively affect the upper respiratory tract), allergic rhinitis, and allergic conjunctivitis.

Examples of tumours are skin neoplasms, mastocytoma and other forms of cellular proliferation, both benign and malignant. It is to be noted that the effectiveness of the present compounds in the prophylaxis and treatment of tumours may arise from properties in addition to 5-lipoxygenase inhibition which also inhibit cell proliferation.

Examples of conditions involving blood platelet aggregation are those resulting from thrombosis, including 'strokes' having a total or partial thrombotic origin, coronary thrombosis, phlebitis and phlebothrombosis (the latter two conditions also possibly being associated with inflammation).

Examples of inflammatory conditions are those of the lungs, joints, eyes, bowel, skin, and heart; particularly those associated with the infiltration of leucocytes into inflamed tissue. Inflammatory lung conditions include asthma, adult respiratory distress syndrome, bronchitis and cystic fibrosis (which may additionally or alternatively involve the bowel or other tissue(s)). Inflammatory joint conditions include rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions. Inflammatory eye conditions include uveitis (including iritis) and conjunctivitis. Inflammatory bowel conditions include Crohn's disease, ulcerative colitis and distal proctitis. Inflammatory skin diseases include those associated with cell proliferation, such as psoriasis, eczema and dermatitis (whether or not of allergic origin). Inflammatory conditions of the heart include coronary infarct damage. Other inflammatory conditions include tissue necrosis in chronic inflammation, endotoxin shock, smooth muscle proliferation disorders (for example, restenosis following angioplasty), and tissue rejection following transplant surgery.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachidonic acid metabolic pathway, for example, a 5-lipoxygenase or cyclooxygenase inhibitor, is indicated; which comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. The present invention further provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, which clinical condition is a spasmogenic condition, an allergic condition, tumour formation, a condition involving blood platelet aggregation, or an inflammatory condition; which comprises administration of a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

In the alternative, there is also provided a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy; particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachidonic acid metabolic pathway, for example, a 5-lipoxygenase or cyclooxygenase inhibitor, is indicated; for example a spasmogenic condition, an allergic condition, tumour formation, a condition involving blood platelet aggregation, or an inflammatory condition.

The amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. A suitable daily dose for a mammal suffering from, or likely to suffer from, any of the clinical conditions described hereinbefore is in the range 0.1μg - 50mg of compound/kilogram bodyweight. In the case of systemic administration, the daily dose is typically in the range 0.05 - 50mg of compound/kilogram bodyweight, the most preferred dosage being from 0.05 to 20mg/kg bodyweight, for example, from 0.1 to 10mg/kg, administered as two or three sub-doses daily. In the case of topical administration, e.g. to the skin or eye, a suitable dose is in the range 0.1μg - 100μg of base per kilogram, typically about 0.1μg/kg.

In the case of oral dosing for the prophylaxis or treatment of airway smooth muscle constriction, for example, in asthma or bronchitis, a suitable dose of the compound of the invention may be as specified in the preceding paragraph, but preferably is from 0.1mg to 10mg of compound/kilogram bodyweight, the most preferred dosage being from 0.1mg to 5mg/kg bodyweight. In the case of pulmonary administration, the dose is typically in the range 2μg - 100mg/kg, preferably, from 5μg to 5mg/kg, for example from 0.01 to 1 mg/kg.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachidonic acid metabolic pathway, for example, a 5-lipoxygenase or cyclooxygenase inhibitor, is indicated; for example a spasmogenic condition, an allergic condition, tumour formation, a condition involving blood platelet aggregation, or an inflammatory condition.

While it is possible for the compound of formula (I), or a salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation. Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The carrier or excipient must, of course, be compatible with the other ingredients in the formulation and must not be detrimental to the recipient. The active ingredient may comprise from 0.1% to 99.9% by weight of the formulation. Typical unit doses of a formulation according to the invention contain from 0.01mg to 1g of the active ingredient. For topical administration, the active ingredient preferably constitutes from 1% to 2% by weight of the formulation, but the active ingredient may constitute as much as 10% w/w. Formulations suitable for nasal or buccal administration, typically contain from 0.1 to 20% w/w, for example, 2% w/w of the active ingredient.

Formulations according to the invention include those in a form suitable for oral, pulmonary, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular and intravenous), intra-articular, topical, or nasal/buccal administration.

The formulations of the invention may conveniently be presented in unit dosage form and may be prepared by any method well known in the art of pharmacy. All such methods include the step of bringing the active ingredient into association with a carrier which constitutes one or more accessory ingredients. Optionally, the particle size of the active ingredient may be reduced before formulation, for example, by micronisation. In general, the formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier, or both, and then, if desired, shaping the product into the required form.

Formulations according to the present invention which are suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or

granules; in the form of a solution, suspension, or a microfine suspension in an aqueous or non-aqueous liquid; or in the form of an oil-in-water or water-in-oil emulsion. The active ingredient may also be in the form of a bolus, electuary, or paste.

A tablet may be made by compressing or moulding the active ingredient, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a disintegrant, compression aid, binder, lubricant, inert diluent, and/or surface active or dispersing agent. Moulded tablets may be made by moulding, in a suitable machine, a mixture of the powdered active ingredient and a suitable carrier moistened with an inert liquid diluent.

Formulations for rectal administration may be in the form of a suppository incorporating the active ingredient and a carrier such as cocoa butter, or in the form of an enema.

Formulations suitable for parenteral administration typically comprise a sterile aqueous or non-aqueous preparation such as an emulsion, suspension, or colloid of the active ingredient which is preferably isotonic with the blood of the recipient. Such formulations may also be freeze-dried and then reconstituted by addition of a sterile fluid shortly before administration.

Formulations suitable for intra-articular administration may be in the form of a sterile aqueous preparation of the active ingredient, which latter may be in microcrystalline form, for example, an aqueous microcrystalline suspension.

Liposomal formulations and biodegradable polymer systems may also be used, for example to present the active ingredient for parenteral, intra-articular and ophthalmic administration.

Formulations suitable for topical administration include liquid and semi-liquid preparations such as liniments, lotions and applications; oil-in-water and water-in-oil emulsions such as creams, ointments and pastes; and solutions and suspensions such as drops. For example, for ophthalmic administration, the active ingredient may be presented as aqueous eye drops, for example, in the form of a 0.1 - 1.0% w/v solution.

Suitable formulations for administration by inhalation include fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols,

nebulisers, or insufflators.

For pulmonary administration via the mouth, the particle size of the powder or droplets is typically in the range 0.5 - 10μm, preferably 1 - 5μm, to ensure delivery into the bronchial tree. For nasal administration, a particle size in the range 10 - 500μm is preferred to ensure retention in the nasal cavity.

Metered dose inhalers are pressurised aerosol dispensers, typically containing a suspension or solution formulation of the active ingredient in a liquefied propellant. During use, these devices discharge the formulation through a valve adapted to deliver a metered volume, typically from 10 to 150μl, to produce a fine particle spray containing the active ingredient. Suitable propellants include certain chlorofluorocarbon compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, anti-oxidants and suitable flavouring agents.

Nebulisers are commercially available devices that transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of a compressed gas through a narrow venturi orifice, typically air or oxygen, or by means of ultrasonic agitation. Suitable formulations for use in nebulisers consist of the active ingredient in a liquid carrier and comprising up to 40% w/w of the formulation, preferably less than 20% w/w. The carrier is typically water or a dilute aqueous alcoholic solution, preferably made isotonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not prepared sterile, for example, methyl hydroxy-benzoate, anti-oxidants, flavouring agents, volatile oils, buffering agents and surfactants.

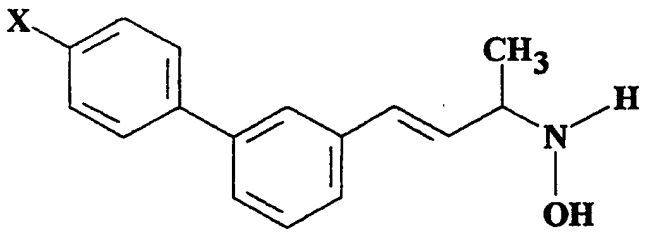
Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the active ingredient, a suitable powder diluent, such as lactose, and an optional surfactant. The active ingredient typically

comprises from 0.1 to 100% w/w of the formulation.

In addition to the aforementioned ingredients, formulations according to the invention may include one or more additional ingredients such as diluents, buffers, flavouring agents, binders, compression aids, disintegrants, surface active agents, thickeners, lubricants, preservatives, for example, methyl hydroxybenzoate, anti-oxidants and emulsifying agents. The compounds of the invention may advantageously be employed in combination with one or more other therapeutic ingredients selected from an antibiotic (for example, an anti-bacterial), anti-fungal, or anti-viral agent, an anti-histamine (particularly a peripherally-acting anti-histamine), or a non-steroidal anti-inflammatory drug (NSAID).

The compounds of these combinations may be administered simultaneously, for example, in the same formulation or in separate formulations, or sequentially within a sufficiently short time interval to achieve the desired combined therapeutic effect. When the compounds are employed in the same formulation, a formulation according to the invention may contain, in addition to a compound of the invention, the further ingredient(s).

According to a further aspect of the invention, there is provided a process for preparing the compounds of formula (I), or salts, solvates, or physiologically functional derivatives thereof which comprises reacting a compound of formula (II)



(II)

either as the (S) enantiomer or a mixture of the (R) and (S) enantiomers, wherein X is as defined for the compound of formula (I), with a suitable agent or agents to effect conversion of the N-hydrogen to an N-C(O)CH_3 group;

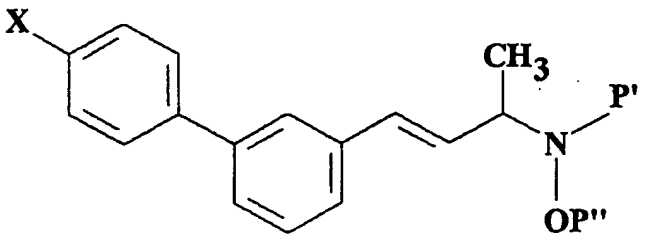
and optionally (a) separating the mixture of enantiomers so obtained and/or (b) converting the compound of formula (I) so formed to a corresponding salt, solvate or physiologically functional derivative thereof.

Conversion of the N-hydrogen to an N-C(O)CH_3 group is typically carried out by treating

a compound of formula (II) with an acylating agent, for example, an appropriate anhydride or activated acid, such as an acid halide, for example, acetyl chloride. This reaction is suitably effected in an inert solvent, such as a halohydrocarbon, for example, dichloromethane, or an alkylbenzene, for example, toluene, at a temperature in the range -10°C to 150°C, for example 0-25°C in the presence of an organic base, such as a trialkylamine, for example, triethylamine. Any N,O-diacylated product of this reaction may be mono-O-deacylated, suitably by treatment with an inorganic base, for example, potassium carbonate, or by treatment with a suitable enzyme, such as a lipase.

Where the compound of formula (II) is present as the (S) enantiomer, the compound of formula (I) may be obtained as the (S) enantiomer. Where the compound of formula (II) is present as a mixture of the (S) and (R) enantiomers, the compound of formula (I) may be obtained as the (S) enantiomer by : (i) separating the enantiomers obtained from the acylation reaction by any suitable method; (ii) effecting the mono-O-deacylation reaction by treatment with an enzyme capable of selectively reacting with the (S) enantiomer, for example a lipase, to produce a mixture of the compound of formula (I) as the (S) enantiomer and the N,O-diacylated (R) enantiomer which can then be separated, for example by chromatography; (iii) effecting the mono-O-deacylation reaction by treatment with an enzyme capable of selectively reacting with the (R) enantiomer, for example a lipase, to produce a mixture of the N,O- diacylated compound of formula (I) as the (S) enantiomer and the N-acylated (R) enantiomer which can then be separated, for example by chromatography. The separated N,O-diacylated product of this reaction may then be mono-O-deacylated by any of the methods described above to yield the compound of formula (I) as the (S) enantiomer.

Compounds of formula (II) and salts thereof may be prepared from the corresponding compound of formula (III)



(III)

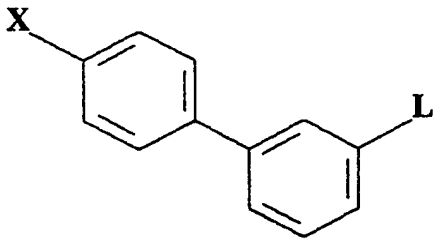
wherein X is as defined for a compound of formula (I), P' is a protecting group, such as an alkoxycarbonyl group, for example, $-CO_2CH_3$, a cyclic ether, for example, tetrahydropyran, or t-butoxycarbonyl (Boc) and P" is a protecting group as described for P' or is hydrogen. The conversion to a compound of formula (II) is suitably effected by acid or base hydrolysis as would be understood by the person skilled in the art. For example, where the -N(Boc)O(Boc) or -N(Boc)OH compound of formula (III) is used, the compound of formula (II), or a salt thereof, may be prepared by treatment with an acid, such as an arylsulphonic acid, for example, para-toluenesulphonic acid; in a non-polar solvent, for example, toluene; at a moderate temperature, suitably in the range 10-100°, for example, 50-60°C. The resulting salt of the compound of formula (II) may then optionally be hydrolysed to release the free base, for example, by chromatography on silica or by treatment with an inorganic base, such as a carbonate, for example, sodium carbonate.

Compounds of formula (III) may be obtained either by:

(i) reaction of the corresponding compound of formula (IV)

$$CH_2=CH-CH(CH_3)-N(P')OP' \qquad (IV)$$

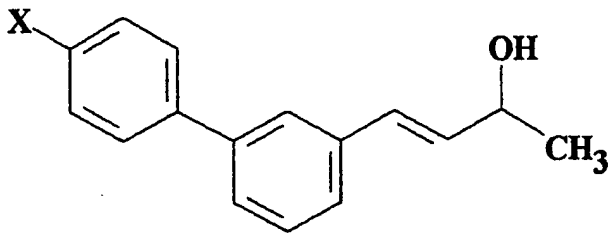
wherein P' is as defined above, with a compound of formula (V)



(V)

wherein X is as defined for the compound of formula (I) and L is a suitable leaving group, for example, a halogen, (typically bromo or iodo) or a substituted sulphonate, for example, trifluoromethanesulfonate; typically at elevated temperature, for example, 50-150°C, in a polar solvent, for example, N,N-dimethylformamide, in the presence of a catalyst, such as palladium (II) acetate with tri(o-tolyl)phosphine, and a suitable base, such as a trialkylamine, for example, triethylamine; or

(ii) reaction of a compound of formula (VI)

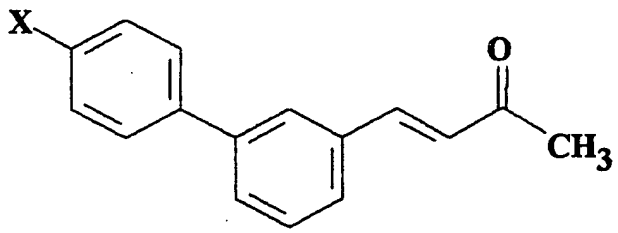


(VI)

wherein X is as defined for formula (I), with a compound of formula HN(P')OP' wherein P' is as defined for the compound of formula (III). This reaction may be effected under Mitsunobu conditions, for example in the presence of diethyl azodicarboxylate (DEAD) or di*iso*propyl azodicarboxylate (DIAD) and triphenylphosphine (PPh_3); in a non-polar solvent, such as toluene; at low temperature, *ie* -20° to 50°C, for example in the region of 0°C. Alternatively, this reaction may be effected by activation of the compound of formula (VI), for example by esterification of the hydroxyl group, typically using an acid anhydride (eg. acetic anhydride) or an acid halide (e.g. chloroacetyl chloride); in the presence of a base (eg. 4-dimethylaminopyridine, DMAP); and a catalyst, for example, tetrakis(triphenylphosphine) palladium (O); in a non-polar solvent, such as tetrahydrofuran (THF); at elevated temperature, for example, 40-120°C.

Compounds of formula (VI) may be prepared either :

(i) by reduction of the corresponding compound of formula (VII)



(VII)

wherein X is as defined for the compound of formula (I). The reduction may be done in such a way that a chiral alcohol of formula (VI) is obtained, for example, (a) by using a chiral inducing catalyst, suitably an oxazaborolidine CBS catalyst (E.J. Corey *et al* Tet Letters 31(5), 611 (1990)) with the reducing agent, suitably catechol borane in an inert solvent, such as a cyclic ether (eg.THF) or an alkylbenzene (eg. toluene) at

low temperature, for example in the range -100°C to 50°C, or (b) by an enzymic reduction process. Alternatively, the reduction may be carried out to give the racemic alcohol of formula (VI) using conventional reducing agents of organic chemistry for example, treatment with sodium borohydride in a polar solvent, such as an alcoholic solvent, at low temperature, for example in the range -50°C to 30°C. If desired, the enantiomeric mixture of compounds of formula (VI) so obtained may be separated into the individual enantiomers by any suitable method, for example, by an enzymic resolution process, typically an enzyme catalysed acyl-transfer or hydrolysis reaction effected by treating the racemic compound of formula (VI) with an acyl donor, such as an enol ester (eg. vinyl acetate), an activated ester (eg. trifluoroethylbutyrate), or an acid anhydride (eg. succinic anhydride),either in the presence of a suitable enzyme capable of acylating only one enantiomer, such as a lipase, in an inert solvent, such as an aromatic solvent (eg. toluene), at non-extreme temperature, for example in the range -20°C to 60°C, or followed by treatment with a suitable enzyme capable of selectively hydrolising one acylated enantiomer, such as a lipase. The resulting enantiomers may then be separated because one of them is present in acylated form, by any appropriate method, for example, by chromatography. If desired, the unwanted enantiomer may be "recycled", for example by racemic deacylation, suitably by hydrolysis; or

(ii) by reaction of the appropriate compound of formula (V) as defined above with a compound of formula (VIII)

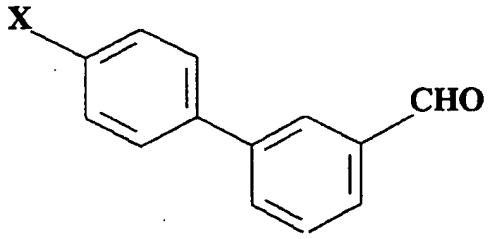
$$CH_2=CH-CH(CH_3)-OP' \qquad \text{(VIII)}$$

wherein P' as hereinbefore defined. This reaction may be carried out in the presence of a suitable catalyst system, for example, palladium (II) acetate/tri-(o-tolyl)phosphine, and a base, such as a trialkylamine, for example, triethylamine. Subsequent removal of the hydroxyl protecting group P' may be effected by any suitable method, such as hydrolysis, for example, acid hydrolysis; or

(iii) by reaction of the appropriate compound of formula (V) as defined above with crotonaldehyde ($CH_3CH=CHCHO$) and then isomerising the resulting allylic alcohol to give the desired compound of formula (VI). The reaction with crotonaldehyde may be carried out typically by lithiation of the compound of formula (V), for example by treatment with butyl lithium at low temperature (suitably below -50°C)

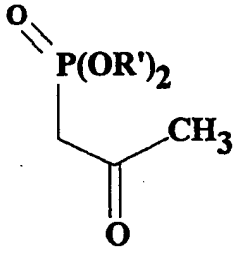
followed by treatment with the crotonaldehyde. The isomerisation may be carried out by treatment with acid, for example hydrochloric acid at moderate temperature.

The compound of formula (VII) may be prepared by reaction of the corresponding aldehyde of formula (IX)



(IX)

wherein X is as defined for the compound of formula (I), with a compound of formula (X)



(X)

wherein R' is C_{1-4} alkyl or, alternatively with acetone; in the presence of a base, such as sodium carbonate; in a polar solvent, such as THF, at a non-extreme temperature, for example -50° to 30°C.

Compounds of formula (VIII) and HN(P')OP' may be prepared from the corresponding commercially available alcohol and hydroxylamine by standard protecting group chemistry.

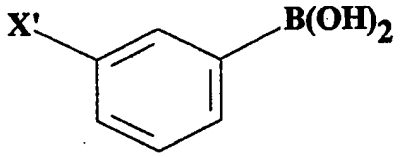
Compounds of formula (IX) may be prepared from compounds of formula (V) as defined above, typically by lithiation (for example with n-butyl lithium at low temperature, *ie* -100° to -20°C) followed by reaction with N,N-dimethylformamide (DMF).

Compounds of formula (X) are commercially available or may be prepared by methods well known to the person skilled in the art or by methods readily available from standard chemical literature.

Compounds of formula (IV) may be obtained by one or more of the methods described in

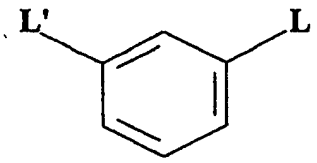
EP 0384594.

Compounds of formula (V) may be obtained commercially or prepared, for example, by coupling a compound of formula (XI)



(XI)

wherein X' is as defined for X in the compound of formula (I), or is a suitable precursor therefor, or a suitably protected form thereof, with a compound of formula (XII)



(XII)

wherein L is as defined above for formula (V) and L' is either the same as L or is a different leaving group as understood by a skilled person. This coupling may suitably be effected in the presence of a suitable catalyst, for example, tetrakis (triphenylphosphine) palladium (0) and an inorganic base, for example, sodium carbonate.

Alternatively, compounds of formula (V) may be prepared by coupling a compound of formula (XII) as hereinbefore defined with the appropriate organometallic reagent (for example, the appropriately substituted PhMgY or PhZnY, where Y is a halogen) which may be prepared *in situ* from the corresponding halide by treatment with the metal (e.g. Mg or Zn). The coupling may be effected in an inert solvent, for example, THF, in the presence of a catalyst, for example, 1,4-bis(diphenylphosphine)butane palladium (0) dichloride, palladium acetate, or tetrakistriphenyl phosphine palladium (0), at non-extreme temperature, for example 0-60°C.

The enantiomeric compounds of the invention may be obtained (a) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods as described above, or preparing and separating suitable diastereoisomers, or (b) by direct synthesis from the appropriate chiral

intermediates by the methods described above.

Optional conversion of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate base. Optional conversion of a compound of formula (I) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I), for example:

(a) Compounds of formula (II) as defined above, or a salt thereof; particularly, a compound selected from:
(E)-N-[3-(4'-Cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine;
(E)-N-[3-(4'-Cyano-3-biphenylyl)-1(R,S)-methyl-2-propenyl]hydroxylamine;
(E)-N-[3-(4'-Fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine;
(E)-N-[3-(4'-Fluoro-3-biphenylyl)-1(R,S)-methyl-2-propenyl]hydroxylamine;
(E)-N-[3-(4'-Chloro-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine; and
(E)-N-[3-(4'-Chloro-3-biphenylyl)-1(R,S)-methyl-2-propenyl]hydroxylamine;

(b) Compounds of formula (III) as defined above; particularly, a compound selected from:
(E)-N,O-Bis(t-butoxycarbonyl)-N-[3-(4'-cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine;
(E)-N,O-Bis(t-butoxycarbonyl)-N-[3-(4'-cyano-3-biphenylyl)-1(R,S)-methyl-2-propenyl]hydroxylamine;
(E)-N,O-Bis(t-butoxycarbonyl)-N-[3-(4'-fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine;
(E)-N,O-Bis(t-butoxycarbonyl)-N-[3-(4'-fluoro-3-biphenylyl)-1(R,S)-methyl-2-propenyl]hydroxylamine;
(E)-N,O-Bis(t-butoxycarbonyl)-N-[3-(4'-chloro-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine; and
(E)-N,O-Bis(t-butoxycarbonyl)-N-[3-(4'-chloro-3-biphenylyl)-1(R,S)-methyl-2-propenyl]hydroxylamine;

(c) Compounds of formula (VI) as defined above; particularly, a compound selected from:

(E)-4-(4'-Cyano-3-biphenylyl)-3-buten-2(S)-ol;
(E)-4-(4'-Cyano-3-biphenylyl)-3-buten-2(R)-ol;
(E)-4-(4'-Cyano-3-biphenylyl)-3-buten-2(R,S)-ol.
(E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2(S)-ol;
(E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2(R)-ol;
(E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2(R,S)-ol.
(E)-4-(4'-Chloro-3-biphenylyl)-3-buten-2(S)-ol;
(E)-4-(4'-Chloro-3-biphenylyl)-3-buten-2(R)-ol; and
(E)-4-(4'-Chloro-3-biphenylyl)-3-buten-2(R,S)-ol.

(d) Compounds of formula (VII) as defined above; particularly,a compound selected from:
(E)-4-(4'-Cyano-3-biphenylyl)-3-buten-2-one;
(E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2-one; and
(E)-4-(4'-Chloro-3-biphenylyl)-3-buten-2-one.

(e) Compounds of formula (IX) as defined above; particularly, a compound selected from:
3'-(4'-Cyanophenyl)benzaldehyde.
3'-(4'-Fluorophenyl)benzaldehyde.
3'-(4'-Chlorophenyl)benzaldehyde.

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

Synthetic Example 1

Preparation of (E)-N-[3-(4'-Cyano-3-biphenylyl)-1(S)-methyl-2-propenyl] acetohydroxamic acid

(a) 4-Cyanophenylboronic acid

A cooled (-100°C), stirred solution / suspension of 4-bromobenzonitrile (9.10 g, Aldrich) in dry tetrahydrofuran (250 ml, Fluka) and under a dry nitrogen

atmosphere, was treated dropwise over 20 minutes with a 1.6M solution of n-butyllithium in hexane (31.3 ml, Fluka). Stirring was continued at -100°C for a further 10 minutes and then the reaction mixture was transferred over 15 minutes into a cooled (-100°C), stirred mixture of tri(*iso*-propyl)borate (23 ml, Aldrich) and dry tetrahydrofuran (2 ml) under a dry nitrogen atmosphere. Stirring was continued at -100°C for a further 10 minutes then the temperature was allowed to rise to 20°C over 1.5 hours.

To the reaction mixture was added 2M hydrochloric acid (50 ml) with vigorous stirring for 30 minutes and then the mixture was extracted with ether (150 ml). The organic layer was separated, washed with water (100 ml) and dried over anhydrous magnesium sulphate. The mixture was filtered and the filtrate evaporated under reduced pressure to yield a beige solid which, on recrystallisation from a minimum volume of boiling water, afforded cream needles (5.50 g); mp > 300°C.

Microanalysis: $C_7H_6BNO_2$ % found (calculated)
C 56.96 (57.21) H 4.14 (4.12) N 9.42 (9.53)

(b) 3-Bromo-4'-cyanobiphenyl

To a vigorously stirred solution of 1,3-dibromobenzene (26.49 g, Fluka) in toluene (610 ml) under a nitrogen atmosphere, was added tetrakis(triphenylphosphine)palladium(0), (1.30 g, Aldrich). Once all the solid had dissolved, a solution of the product from Example 1(a) (5.50 g) in a minimum volume of ethanol was added, followed by a 2M aqueous solution of sodium carbonate (41 ml). The vigorously stirred mixture was then heated under reflux for 19 hours with the exclusion of light.

The reaction mixture was cooled to room temperature, diluted with water (100 ml) and the layers were separated. The aqueous layer was extracted with fresh toluene (100 ml) and the organic layers were then combined, washed with water (2 x 250 ml), dried over anhydrous magnesium sulphate and filtered. Evaporation under reduced pressure gave a yellow oil which was purified by silica gel column chromatography, eluting firstly with petroleum ether bp 40-60°C then with diethyl ether/petroleum ether bp 40-60°C (2:1) to give the pure product as a colourless solid (4.50 g) together with some slightly impure product as a pale yellow solid

(2.44 g).

IR gave an intense peak at 2224 cm^{-1} (CN stretch)

Mass Spectrometry (EI : $(M+1)^+$ at 257 and 259

Microanalysis: $C_{13}H_8BrN$ % found (calculated)
C 62.16 (60.49) H 3.22 (3.12) N 5.44 (5.43)

(c) (E)-N,O-Bis(t-butoxycarbonyl)-N-[3-(4'-cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine

To a stirred solution of the product from Example 1(b) (4.50g) and N,O-bis(t-butoxycarbonyl)-N-but-1-en-3(S)-ylhydroxylamine prepared as described in EP 0384594 (Synthetic Examples 2 and 3) (5.01g), in dry N,N-dimethylformamide (17.5ml) and under a dry nitrogen atmosphere, was added triethylamine (3.91g, Aldrich) followed by tri(o-tolyl)phosphine (215 mg, Aldrich) and palladium (II) acetate (78 mg, Lancaster). The stirred mixture was heated at 100°C, with exclusion of light, for 11 hours then cooled to room temperature.
The reaction mixture was poured into water (250 ml) with stirring for 5 minutes, and then the mixture was extracted with ethyl acetate (3 x 100 ml). The extracts were combined, washed with water (3 x 150 ml), dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated under reduced pressure to give a tan, viscous oil (7.66g) which was used without further purification.

(d) (E)-N-[3-(4'-Cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine

A solution of crude product from Example 1(c) (7.66g) and toluene-4-sulphonic acid monohydrate (4.14g, B.D.H.) in methanol (120 ml) was heated under gentle reflux for 45 minutes then cooled to room temperature. The solution was evaporated under reduced pressure and the residue treated with saturated aqueous sodium hydrogen carbonate solution (50ml) then extracted into ethyl acetate (3 x 150 ml). The combined extracts were washed with water (2 x 150 ml), dried over anhydrous magnesium sulphate and filtered. The filtrate was evaporated under reduced pressure to give a tan gum (4.60g) which was used without further purification.

(e) (E)-O-Acetyl-N-[3-(4'-cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]-acetohydroxamate

A stirred solution of crude product from Example 1(d) (4.60g), pyridine (3.03g) and 4-(dimethylamino)pyridine (50mg) in dichloromethane (100ml) was cooled in an ice bath with the exclusion of moisture. A solution of acetyl chloride (3.01g) in dichloromethane (10ml) was added dropwise over 20 minutes, then stirring was continued at 0°C for 30 minutes then at room temperature for 16 hours.

The reaction mixture was evaporated under reduced pressure, the residue dissolved in ethyl acetate (250ml) and the solution washed with 2M hydrochloric acid (2 x 100ml) then with saturated aqueous sodium hydrogen carbonate solution (100ml) and finally with water (100ml). The organic layer was dried over anhydrous magnesium sulphate, filtered and the filtrate evaporated under reduced pressure to give a tan gum. The product (2.26g) was isolated as a pale yellow gum by silica gel column chromatography, eluting with diethyl ether.

(f) (E)-N-[3-(4'-Cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid

A solution of the product of Example 1(e) (2.26g), in methanol (75ml) was cooled in an ice bath with the exclusion of moisture, then anhydrous potassium carbonate (1.79g) was added with stirring at 0°C for 1 hour.

The reaction mixture was evaporated under reduced pressure and the residue treated with water (100ml) followed by acidification with citric acid. The mixture was extracted with ethyl acetate (3 x 100ml) and the combined extracts were then washed with water (2 x 150ml) and dried over anhydrous magnesium sulphate. The mixture was filtered and the filtrate evaporated under reduced pressure to give a pale orange gum from which the product (1.18g) was isolated as a pale yellow gum by silica gel column chromatography, eluting with diethyl ether. Trituration with diethyl ether/petroleum ether bp 40-60°C gave a solid which was then recrystallised from ethyl acetate / ether (1:4) to give the product (0.94g) as a cream solid; mp 127-129°C.

200 MHz ^{1}H-NMR ($DMSOd_6$) δ : 9.5 (s, 1H, OH), 8.0 - 7.4 (m, 8H, ArH) , 6.7 -

6.3 (m, 2H, vinyl-H), 5.3 - 5.1 (m, 1H, methine-H), 2.05 (s, 3H, acetyl-H), 1.35 - 1.25 (d, 3H, methyl-H) .

IR gave intense peaks at 2222 cm^{-1} (CN stretch) and 1597 cm^{-1} (CO stretch)

$[\alpha]_D^{23} = -149.16^o$ $[\alpha]_{Hg546}^{23} = -184.41^o$ (c = 1.0, ethanol)

Microanalysis: $C_{19}H_{18}N_2O_2$ % found (calculated)
C 74.21 (74.49) H 5.90 (5,92) N 8.98 (9.15)

Synthetic Example 2

Preparation of (E)-N-[3-(4'-fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]-acetohydroxamic acid

(a) 4-fluorophenylboronic acid

A stirred solution of 4-fluorobromobenzene (105g) in dry tetrahydrofuran (THF) (500ml) under nitrogen was cooled to -70°C and then a 1.6M solution of butyllithium in hexane (375ml) was added slowly, keeping the temperature below -67 °C. Stirring was then continued at -70°C for 10 minutes before pumping the mixture gradually into a stirred mixture of tri(isopropyl)borate (277ml) and dry THF (100ml) under nitrogen at -70°C. After the addition, the reaction mixture was stirred at -70° C for 10 minutes before being allowed to warm to ambient temperature. 2M aqueous hydrochloric acid (300ml) was then added and the reaction was stirred for a further 30 minutes.

The reaction mixture was diluted with diethyl ether (125ml) and the resulting aqueous layer was separated and washed with diethyl ether (2x125ml). The combined ethereal solutions were washed with water and dried over $MgSO_4$. Removal of the solvent gave the title compound as a cream solid (78.5g).

(b) 3-Bromo-4'-fluorobiphenyl

To a stirred solution of 1,3-dibromobenzene (397g) in toluene (3.0 litres) under nitrogen, was added tetrakis (triphenylphosphine) palladium (0) (16.5g). A solution

of the product from Example 2(a) (78.5g) in absolute ethanol (500ml) was then added followed by 2M aqueous Na_2CO_3 (561ml).

The vigorously stirred reaction mixture was then refluxed for 11 hours under nitrogen. On cooling, the separated toluene layer was washed with water (2 x 500ml) and dried over $MgSO_4$. Distillation afforded the title compound (85-90 °C/0.1mbar).

(c) N,O-Bis(t-butoxycarbonyl)-N-[3-(4'-fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]-hydroxylamine

To a stirred mixture of the product from Example 2(b) (63.49g) and N,O-Bis(t-butoxycarbonyl)-N-(but-3-en-2(S)-yl]hydroxylamine prepared as described in EP 0384594 (Synthetic examples 2 and 3) (72.60g), and dry N,N-dimethylformamide (DMF) (250ml) under nitrogen, was added triethylamine (56.66g), tri(o-tolyl)phosphine (3.11g) and then palladium (II) acetate (1.14g). The stirred reaction mixture was then heated at 100°C for 9 hours.

On cooling, the reaction mixture was poured into water (2.5 litres), and extracted with diethyl ether (4x500ml). The combined ether extracts were then washed with water (3x500ml), dried over $MgSO_4$, and treated with charcoal. Removal of the solvent gave the title compound (110.2g).

(d) (E)-N-[3-(4'-fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]hydroxylamine

A solution of the product from Example 2(c) (0.253mol) in methanol (1000ml) was treated with toluene-4-sulphonic acid monohydrate (60.09g) and then refluxed for 105mins.

The cooled reaction mixture was evaporated under reduced pressure, the residue was treated with excess saturated aqueous $NaHCO_3$ and extracted with diethyl ether (3x300ml). The combined ether extracts were dried over $MgSO_4$ before removing the solvent under reduced pressure to give the title compound as a tan oil.

(e) (E)-N-[3-(4'-fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid

A stirred solution of the product from Example 2(d) (43.97g) in dichloromethane (1000ml) was cooled to 0°C with the exclusion of moisture. 4-dimethylaminopyridine (1.0g) was added, followed by dropwise addition of acetyl chloride (41.71g). Stirring was continued at 0°C for 45 minutes then at room temperature for 14 hours.

The reaction mixture was evaporated under reduced pressure and the residue was partitioned between diethyl ether (750ml) and 2M HCl (500ml). The separated aqueous phase was washed with diethyl ether (750ml) and the combined ether fractions washed successively with 2M HCl, saturated $NaHCO_3$ and water before dried on MgSO4. Evaporation *in vacuo* followed by flash chromatography (SiO_2, diethyl ether/40-60°C petroleum ether 2:1) afforded the bis-acetyl compound.

Anhydrous K_2CO_3 (32.93g) was added to a solution of the bis-acetyl compound (40.68g) in methanol (600ml), cooling in an ice-bath. The reaction was stirred for 1 hour at 0°C with the exclusion of moisture then evaporated *in vacuo.*

The residue was treated with water (500ml) then acidified with citric acid and extracted with diethyl ether (3x300ml). The combined ether extracts were washed with water (2x500ml) and dried over $MgSO_4$. Removal of the solvent gave the crude title product as an orange oil (37.36g). Purification by flash chromatography (SiO_2, diethyl ether) and recrystallisation from 40-60°C Petroleum ether/diethyl ether gave the title compound as a white fluffy solid, mp 72-76°C;

Microanalysis: $C_{18}H_{18}FNO_2$. 0.6 H_2O found (calculated) %:
C 69.77 (69.70), H 6.12 (6.24), N 4.55 (4.52);

Optical rotation (c=1.0, EtOH): $[\alpha]_D^{22} = -162.26°$, $[\alpha]_{Hg546}^{22} = 200.99°$.

(f) Anhydrous form of (E)-N-[3-(4'-Fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl] acetohydroxamic acid

The product from Example 2(e) (100 mg) was heated at 40°C and 0.05 mbar for 1 hour. The temperature was raised to 55°C for a further 1 hour, then to 80°C for 3 hours. Heating was removed and the melt allowed to return to room temperature before the vacuum was released. The colourless, glassy residue was triturated with a 2:1 mixture of diethyl ether and petroleum ether bp 40-60°C (5 ml) to yield a

colourless, feathery, crystalline solid (70 mg); mp 115-117°C.

200 MHz ^{1}H-NMR (DMSOd_6) δ : 9.25 (s, 1H, OH), 7.8 - 7.2 (m, 8H, ArH), 6.7-6.3 (m, 2H, vinyl-H), 5.3 - 5.1 (m, 1H, methine-H) , 2.0 (s, 3H, acetyl-H), 1.4-1.2 d, 3H, methyl-H).

FAB-Mass Spectrometry : $(M+1)^+$ at 300, $(M+Na)^+$ at 322

$[\alpha]_D^{24.5}$ = -172.3°, $[\alpha]_{Hg546}^{24.5}$= -213.5° (c=1.0, EtOH)

Microanalysis: $C_{18}H_{18}FNO_2$ % found (calculated)

C 72.04 (72.22) H 6.04 (6.06) N 4.54 (4.68)

Synthetic Example 3

Preparation of (E)-N-[3-(4'-Chloro-3-biphenylyl)-1(S)-methylprop-2-enyl]-acetohydroxamic acid

(a) 3-Bromo-4'-chlorobiphenyl

4-Chlorobenzeneboronic acid (3.13g, 20mmol) was added to a solution containing 1-bromo-3-iodobenzene (5.66g 20 mmol) and tetrakis (triphenylphosphine)palladium(0) (250mg) in THF (60ml), under nitrogen. Deoxygenated water (60ml) was then added, followed by sodium carbonate (4.24g, 40mmol). The mixture was heated at reflux under nitrogen for 16 h. After cooling, ether was added and the two phases separated. The organic phase was washed with water and saturated brine, dried over sodium sulphate and the solvent removed. The residue was taken up in hexane and filtered to remove some insoluble solid. The hexane was evaporated and the product purified by chromatography on silica, eluting with cyclohexane, to give 3-bromo-4'-chlorobiphenyl (3.63g, 68%) as a colourless oil.

(b) (E)-N,O-Bis (t-butoxycarbonyl)-N-[3-(4'-chloro-3-biphenylyl)-1(S)-methylprop-2-enyl]hydroxylamine and (E)-N-(t-butoxycarbonyl)-N-[3-(4'-chloro-3-biphenylyl)-1(S)-methylprop-2-enyl] hydroxylamine

To the product from Example 3(a) (2.68g, 10mmol) and (S)-N,O-bis(t-butoxycarbonyl)-N-but-3-en-2-ylhydroxylamine (3.16g, 11mmol) in dry DMF (40ml) was added triethylamine (3.06ml, 22mmol) followed by tri(o-tolyl)phosphine (304mg, 1mmol) and finally palladium acetate (112mg, 0.5mmol). The mixture was heated, under N_2, at 110-120°C for 8 h. After cooling, the mixture was poured into water and extracted with ethyl acetate. The extracts were washed with water (3x), then with saturated brine, dried (Na_2SO_4) and the solvent evaporated, giving a brown gum. The residue showed two major components on TLC, Rf 15 0.43 and 0.22 (EtOAc-cyclohexane, 1:4). They were separated by column chromatography, eluting with ethylacetate-cyclohexane, (1:6). The first eluted compound (1.64g) was the N,O-bis(t-butoxycarbonyl) product and the slower-running component (1.74g) was the N-mono(t-butoxycarbonyl) compound. Both compounds were gums, containing impurities by NMR and were combined and used directly in the following step.

(c) (E)-N-[3-(4'-Chloro-3-biphenylyl)-1(S)-methylprop-2-enyl]hydroxylamine

The combined mono- and bis-(t-butoxycarbonyl) compounds from the previous reaction (total of 3.34g) were dissolved in toluene (50ml) and p-toluenesulphonic acid (1.52g, 9mmol) added. The mixture was stirred and heated at 55-60°C for 3h. After cooling, it was washed with aqueous sodium bicarbonate, then with saturated brine. Drying (Na_2SO_4) followed by solvent removal gave a gum which was purified by chromatography on silica, eluting with dichloromethane-methanol (20:1). The pure hydroxylamine was obtained as a pale yellow oil which slowly solidified (0.86g).

(d) (E)-N,O-bis(acetyl)-N-[3-(4'-chloro-3-biphenylyl)-1(S)-methyl prop-2-enyl]-hydroxylamine

The product from Example 3(e) (0.84g, 3.07mmol) in dichloromethane (25ml) was stirred at 0°C under dry N_2 as pyridine (0.57ml, 7mmol) was added, followed by acetyl chloride (0.50ml, 7mmol), added dropwise. The mixture was stirred for 16h, allowing to slowly warm to room temperature. The mixture was washed with water and saturated brine, dried (Na_2SO_4) and the solvent evaporated. Purification was achieved by chromatography on silica (ethyl acetate-cyclohexane, 1:2), giving the

required product as a colourless gum (0.95g, 86%).

(e) (E)-N-[3-(4'-Chloro-3-biphenylyl)-1(S)-methylprop-2-enyl]acetohydroxamic acid

The product from Example 3(d) (0.93g, 2.60mmol) was stirred in methanol (25ml) at O°C. Potassium carbonate (414mg, 3mmol) was added, and the mixture stirred for 4h. The solvent was evaporated and the residue partitioned between ethyl acetate and 1M HCl. The organic layer was separated, washed with water (2x), then saturated brine, dried (Na_2SO_4) and the solvent evaporated, giving, initially, a gum, which crystallised upon dissolution in ether and scratching. The pure hydroxamic acid was filtered off, washed with ether and dried (0.63g 77%). mp. 109-111°C. MS M/z 315,317 (M^+)

Microanalysis: Calcd: C, 68.46; H, 5.75; N, 4.44%
Found: C, 68.33; H, 5.67; N, 4.37%.

Synthetic Example 4

(a) 3-(4'-Fluorophenyl)benzaldehyde

To a solution of the product from Example 2(b) (5.0g) in THF (50ml), under nitrogen, was added n-butyl lithium (1.6M solution in hexane, 12.5ml), maintaining a temperature of around -70°C. DMF (1.55ml) was then added slowly keeping the temperature in the range -73° to -53°C.

After warming to room temperature, saturated ammonium chloride solution (150ml) was added and the mixture was extracted with diethyl ether (3 x 50ml). The combined ethereal extracts were washed with water then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the product as a pale yellow oil.

(b) (E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2-one

A mixture of the product from Example 4(a) (4.0g), dimethyl-(2-oxopropyl) phosphonate (2.76ml), anhydrous potassium carbonate (5.5g) in THF (60ml) was stirred at around 60°C under nitrogen until reaction was complete. The reaction mixture was filtered, concentrated, then purified by column chromatography on

silica, eluting with ethyl acetate/hexane to afford the crude title compound. Recrystallisation from ethyl acetate/hexane gave the product as a white crystalline solid, mp 67-68°C.

Microanalysis: C 79.77 (79.98), H 5.48 (5.45)

(c) (E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2-(S)-ol

To a solution of the product from Example 4(b) (0.5g) and butyl diphenyl CBS catalyst (0.066g) in toluene (20ml), under an atmosphere of nitrogen, was added catechol borane (1M solution in toluene, 4.16ml) ensuring that the internal temperature was kept below - 55°C. Upon complete addition the resulting yellow solution was stirred at -55°C for 18 hours.

After warming to room temperature, 40% sodium hydroxide solution (20ml) and diethyl ether (50ml) were added and the mixture washed with 40% sodium hydroxide solution (3x10ml) and water (15ml). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the product as a viscous oil (0.38g) which rapidly solidified. The product was determined to have an 80% enantiomeric excess by chiral HPLC methodology.

(d) (E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2-(S)-ol (Alternative method)

Under an atmosphere of nitrogen, to a stirred and cooled (ca. 0°C) suspension of the product from Example 4(b) (10g, 0.0416mol) in SVM (95% ethanol/ 5% methanol) (100ml) was added sodium borohydride (1.56g, 0.041mol) portionwise. The reaction was stirred at 0°C for 2 hours and then quenched into water (300ml).

SVM was removed *in vacuo* and the aqueous residue was extracted with diethyl ether (3.75ml). The combined ether exctracts were washed with water (2.100ml), brine (100ml) and dried over magnesium sulphate. The solution was concentrated to a pale yellow oil (10.66g) which solidified on standing. Crystallisation from diethyl ether/hexane yielded (E)-4-(4'-fluoro-3-biphenylyl)-3-buten-2-ol as a white crystalline solid (8.12g, 80% yield). Melting point = 53-54°C.

The racemic alcohol (3g, 0.0124mol), toluene (30ml), vinyl acetate (5.33g,

0.0619mol) and Amano lipase PS (0.3g, from *Pseudomonas fluorescens*) were stirred together at room temperature for 72 hours. The reaction was filtered through Hyflo and concentrated to a yellow oil. Column chromatography was used to separate the title product from the corresponding O-acetylated (R) enantiomer.

(E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2-(S)-ol was obtained as a white solid (1.39g, 46.3% yield) Mpt = 52-53°C, with a 99.6% enantiomeric excess.
Microanalysis C 78.95 (79.31), H 6.35 (6.24), F 7.97 (7.84).

3-(R)-O-Acetoxyl-1-(3',4-fluorobiphenylyl)-but-2-ene was obtained as a yellow oil (1.63g, 46.2% yield), with a 99.9% enantiomeric excess.
Microanalysis C 75.87 (76.03), H 5.92 (6.03), F 6.86 (6.63).

(e) (E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2-(R)-ol

A solution of the O-acetylated product from Example 4(d) (25g) in methanol (120ml) and 40% sodium hydroxide solution (30ml) was cooled at 0°C and stirred for 90 minutes. Methanol was removed *in vacuo* and the residue partitioned between diethyl ether and water. The resulting aqueous layer was extracted with diethyl ether (3.150ml) and the combined extracts were washed water water (2x100ml), and brine (100ml). The solvent was dried over magnesium sulphate and the solvent removed *in vacuo* to leave a pale oil (19.42g). The oil was crystalised from diethyl ether/hexane to give a white solid. The product alcohol was determined to have a 97.1% enantiomeric excess by chiral HPLC methodology.

(f) Racemisation of (E)-4-(4'-Fluoro-3-biphenylyl)-3-buten-2-(R)-ol

A solution of the alcohol product from Example 4(e) (49.1g) in THF (1000ml) and 2N hydrochloric acid (500ml) was stired at room temperature for 72 hours. The reaction mixture was diluted with water (1000ml) and diethyl ether (1000ml) and the resulting aqueous layer extracted with diethyl ether (500ml). The combined organic layer was washed with water (500ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to leave a yellow oil (51.2g). The oil was determined to be a racemic mixture by chiral HPLC methodology. This material can then be 'recycled' by using it in the process described in Example 4(d).

(g) 3-(S)-O-(chloroacetoxy)-1-(3',4-fluorobiphenylyl)-but-2-ene

A solution of the product from Example 4(d) (0.5g), pyridine (0.31ml), and 4-dimethylaminopyridine (ca. 1mg) in THF (10ml) was cooled to 0°C under an atmosphere of nitrogen. A solution of chloroacetyl chloride (0.19ml) in THF (5ml) was added dropwise to the solution at such a rate as to maintain the temperature at 0°C. The resulting solution was stirred at ca. 0 to -4°C for 18 hours.

The reaction mixture was allowed to warm to room temperature and was diluted with water (50ml). The resulting organic phase was washed with water (50ml) diluted with toluene (50ml) and solvent removed under reduced pressure to leave a colourless oil. This oil was purified by column chromatography to give the product as a viscous colourless oil (0.49g).

(h) O-(tetrahydropyran-2-yl)-N-[1-(4'-fluoro-3-biphenylyl)but-1-en-3-(S)-yl]-hydroxylamine

Bis[dibenzylideneacetone] palladium (0.181g), lithium chloride (0.013g) and triphenylphosphine (0.165g) were dissolved in degassed, peroxide free THF/DMF (1:1v/v, 60ml) under an atmosphere of dry nitrogen. The mixture was stirred at 70°C for 45 minutes before a solution of the product from Example 4(g) (5g) in THF/DMF (1:1v/v, 10ml) under an atmosphere of nitrogen, was added dropwise. The resulting mixture was stirred at 70°C for 1 hour before a solution of O-tetrahydropyran-2-ylhydroxylamine (3.67g) in THF/DMF (1:1v/v, 10ml) under an atmosphere of nitrogen, was added dropwise. The reaction mixture was stirred at 70°C for 48 hours.

The mixture was diluted with diethyl ether (50ml) and water (50ml) and the aqueous layer extracted with diethyl ether (50ml). The combined organic layers were washed with water (50ml), dried over magnesium sulphate, and concentrated to leave a yellow oil (5.6g). The oil was purified by column chromatography to give the product as a viscous colourless oil (2.86g).

(i) O-(tetrahydropyran-2-yl) N-acetyl,N-{1-(4'-fluoro-3-biphenylyl)but-1-en-3-(S)-yl] hydroxylamine

To a solution of the product from Example 4(h) (1.95g) in dry triethylamine (20ml) at 0°C was added a solution of acetyl chloride (0.8g) in dichloromethane (20ml), ensuring that the temperature did not rise above 0°C. The mixture was warmed to room temperature over 14 hours and the reaction mixture was poured into water (50ml). The aqueous phase was extracted with ethyl acetate (4 x 50ml) and the combined organic extracts were dried over magnesium sulphate and concentrated to give the product as a gum (2.1g).

(j) (E)-N-[3-(4'-fluoro-3-biphenylyl)-1(S)-methyl-prop-2-enyl]acetohydroxamic acid

To a solution of the product from Example 4(i) (1.90g) in absolute ethanol (100ml) was added Amberlyst H15 (2.0g). The mixture was stirred at room temperature for 48 hours and the Amberlyst H15 was removed by filtration, the filtrate was treated with anhydrous potassium carbonate (0.2g) and the resulting mixture was concentrated under reduced pressure to leave an oily residue. Water (50ml) was added and the aqueous layer was extracted with ethyl acetate (4 x 50ml). The combined extracts were dried over magnesium sulphate and concentrated to leave an oily residue. The residue was crystallised from diethyl ether/petroleum ether (60-80) after column chromatography to give the product as a white solid (0.25g).

Synthetic Example 5

Preparation of (S)-(E)-N-2-[4-(4'-Fluoro-3-biphenylyl)-but-3-enyl]-O-(ethoxycarbonyl-methylaminocarbonyl) acetohydroxamic acid

The product from Example 2(e) (0.299g, 1mmol) was dissolved in dry THF (5ml) under nitrogen and N-methylmorpholine (0.202g, 0.220ml, 2mmol) was added in one portion, followed by ethyl isocyanatoacetate (0.129g, 0.112ml, 1mmol). The mixture was stirred at room temperature overnight, then was partitioned between ethyl acetate and 1N hydrochloric acid. The organic phase was separated, washed with saturated brine, dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo*. Chromatographic purification of the crude produce on silica, with 1:1 ethyl acetate:cyclohexane eluent gave the title compound (0.257g, 52%) as a waxy solid.

N.m.r. spectrum (200MHz in DMSO-d_6) δ : 1.16 (3H,t), 1.33 (3H,d), 2.01 (3H, s),

3.81 (2H, d), 4.07 (2H, m), 5.23 (1H, m), 6.32-6.68 (2H, m), 7.22-7.79 (8H, m), 8.35 (1H, t).

PHARMACEUTICAL FORMULATION EXAMPLES

The "active ingredient" in the following formulations is as defined above; preferably one of the compounds of Synthetic Examples 1 to 4.

Example A: Oral Tablet (i)

	Per tablet
Active Ingredient	50.0 mg
Lactose	61.0 mg
Sodium Starch Glycollate	10.0 mg
Povidone	3.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient, lactose and sodium starch glycollate . Granulate the powders using a solution of povidone in purified water. Dry the granules, add the magnesium stearate and compress to produce tablets.

Example B: Ointment

Active Ingredient	1.0 g
White Soft Paraffin	to 100.0 g

Disperse the active ingredient in a small volume of the vehicle. Gradually incorporate this into the bulk to produce a smooth, homogeneous product. Fill into collapsible metal tubes.

Example C: Cream for topical use

Active Ingredient	1.0 g
Polawax GP 200	20.0 g
Lanolin Anhydrous	2.0 g
White Beeswax	2.5 g
Methyl hydroxybenzoate	0.1 g
Distilled Water	to 100.0 g

Heat the Polawax, beeswax and lanolin together at 60°C. Add a solution of methyl hydroxybenzoate. Homogenise using high speed stirring. Allow the temperature to fall to 50°C. Add and disperse the active ingredient. Allow to cool with slow speed stirring.

Example D: Lotion for topical use

Active Ingredient		1.0 g
Sorbitan Monolaurate		0.6 g
Polysorbate 20		0.6 g
Cetostearyl Alcohol		1.2 g
Glycerin		6.0 g
Methyl Hydroxybenzoate		0.2 g
Purified Water B.P.	to	100 ml

The methyl hydroxybenzoate and glycerin were dissolved in 70ml of the water at 75°C. The sorbitan monolaurate, Polysorbate 20 and cetostearyl alcohol were melted together at 75°C and added to the aqueous solution. The resulting emulsion was homogenised, allowed to cool with continuous stirring and the active ingredient added as a suspension in the remaining water. The whole was stirred until homogeneous.

Example E: Oral Tablet (ii)

	Per tablet
Active Ingredient	10.0 mg
Lactose	80.0 mg
Microcrystalline Cellulose	40.0 mg
Povidone	4.0 mg
Sodium Starch Glycollate	15.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient and microcrystalline cellulose before blending with lactose, povidone and sodium starch glycollate. Lubricate with magnesium stearate and compress to produce tablets (150mg per tablet).

Example F: Oral capsule

Active Ingredient	25.0 mg
Starch 1500	100.0 mg
Sodium Starch Glycollate	14.0 mg
Magnesium Stearate	1.0 mg

Mix together the active ingredient, Starch 1500 and sodium starch glycollate before blending with magnesium stearate. Fill power into Size 3 capsule shells (140 mg per capsule).

Example G: Powder capsules for inhalation

Active Ingredient (0.5-7.0μm powder)	1.0 mg
Lactose (30-90μm powder)	49.0 mg

The powders were mixed until homogeneous and filled into suitably sized hard gelatin capsules (50mg per capsule).

Example H: Inhalation aerosol

Active Ingredient (0.5-7.0μm powder)	50.0 mg
Sorbitan Trioleate	100.0 mg
Saccharin Sodium (0.5-7.0μm powder)	5.0 mg
Methanol	2.0 mg
Trichlorofluoromethane	4.2 g
Dichlorodifluoromethane	to 10.0 ml

The sorbitan trioleate and menthol were dissolved in the trichloro-fluoromethane. The saccharin sodium and active ingredient were dispersed in the mixture which was then transferred to a suitable aerosol canister and the dichlorofluoromethane injected through the valve system. This composition provides 0.5mg of active ingredient in each 100μl dose.

BIOLOGICAL DATA

In vitro inhibition of 5-lipoxygenase

Leukocytes were isolated from blood donated by normal aspirin-free volunteers by washing and centrifugation. A solution of the test compound in DMSO (10μl, final concentration 0.01 - 100μM) was added to the washed cell suspension (480μl) and the mixture incubated at room temperature for 5 minutes. The tubes were placed on ice for 5 minutes and then stimulated with the calcium ionophore A-23187 (10μl, final concentration 2.0μM) for 5 minutes at 37°C. The reaction was terminated by boiling and the plasma concentration of LTB4 determined by Scintillation Proximity Assay (SPA).

Each of the compounds of Synthetic Examples 1 to 4, when tested in this screen, was found to have an average IC_{50} of less than 1μM.

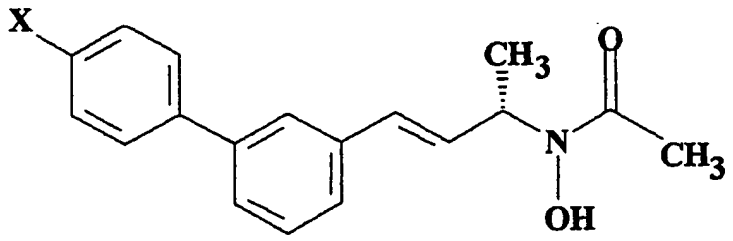
In Vitro inhibition of cyclooxygenase

Washed platelet suspensions from healthy human donors were prepared according to the method of Radomski et al (Thromb. Res., 30, 383-393, 1983). Tubes containing aliquots (0.5ml) of platelet suspension (10^7 cells/ml) were incubated with test drug or vehicle for 5 minutes at room temperature before being placed on an ice bath for a further 5 minutes. The calcium ionophore A-23187 was added (final concentration 2μM) and the tubes were incubated for 5 minutes at 37°C. The reaction was terminated by boiling for 2 minutes and the cellular precipitate removed for centrifugation. The thromboxane B_2 content of the supernatant was determined by radio-immunoassay.

Each of the compounds of Synthetic Examples 1 to 4, when tested in this screen was found to have an average IC_{50} of less than 10μM.

CLAIMS

1. A compound of formula (I)



(I)

wherein X is cyano, fluoro, or chloro;
or a salt, solvate, or physiologically functional derivative thereof.

2. A compound selected from:
(E)-N-[3-(4'-Cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid;
(E)-N-[3-(4'-Fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid;
(E)-N-[3-(4'-Chloro-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid;
and salts, solvates and physiologically functional derivatives thereof.

3. A compound according to claim 1 or 2 which is:
(E)-N-[3-(4'-Cyano-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid.

4. A compound according to claim 1 or 2 which is:
(E)-N-[3-(4'-Fluoro-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid.

5. A compound according to claim 1 or 2 which is:
(E)-N-[3-(4'-Chloro-3-biphenylyl)-1(S)-methyl-2-propenyl]acetohydroxamic acid.

6. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachidonic acid metabolic pathway is indicated; which comprises administration of a therapeutically effective amount of a compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

7. A method according to claim 6 wherein the clinical condition is selected from asthma, ulcerative colitis, and irritable bowel syndrome.

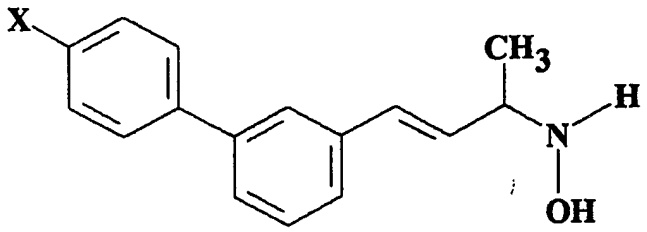
8. A compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

9. A compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in the treatment of a medical condition selected from asthma, ulcerative colitis, and irritable bowel syndrome.

10. Use of a compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which an inhibitor of the lipoxygenase or cyclooxygenase mediated arachidonic acid metabolic pathway is indicated.

11. A pharmaceutical formulation comprising a compound of formula (I) according to any one of claims 1 to 5, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

12. A process for preparing a compound of formula (I), or a salt, solvate, or physiologically functional derivative thereof, which comprises reacting a compound of formula (II)

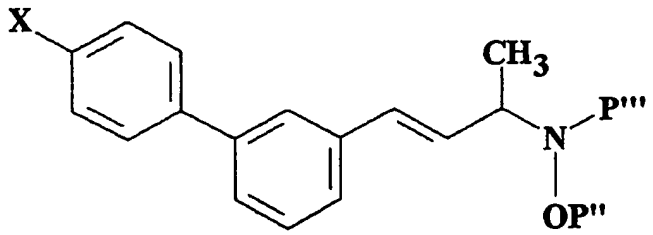


(II)

either as the (S) enantiomer or a mixture of the (R) and (S) enantiomers, wherein X is cyano, fluoro, or chloro, with a suitable agent or agents to effect conversion of the N-hydrogen to an N-C(O)CH_3 group;

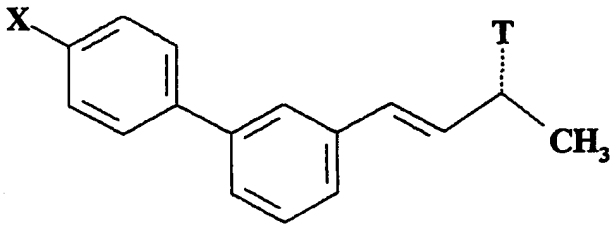
and optionally (a) separating the mixture of enantiomers so obtained and/or (b) converting the compound of formula (I) so formed to a corresponding salt, solvate or physiologically functional derivative thereof.

13. A compound of formula



wherein X is cyano, fluoro, or chloro and either : (i) P'' and P''' are both hydrogen, or (ii) P'' is hydrogen or a protecting group and P''' is a protecting group; or a salt thereof.

14. A compound of formula



wherein X is cyano, fluoro, or chloro and either (i) the dotted line represents a single bond and T is a hydroxyl group, or (ii) the dotted line represents a double bond and T is oxo.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 94/00886

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C259/06 C07C275/64 A61K31/16 A61K31/17 C07C239/10
C07C239/22 C07C255/56 C07C255/53 C07C255/64 C07C49/235
C07C33/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 196 184 (THE WELLCOME FOUNDATION) 1 October 1986 cited in the application see page 9, column 13, line 21 - line 38; claims ---	1-12
Y	EP,A,0 351 214 (THE WELLCOME FOUNDATION) 17 January 1990 see page 2, line 50 - line 53 see page 3, line 28 - page 4, line 20 --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 1994	09. 08. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Seufert, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 94/00886

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ADVANCES IN PROSTAGLANDIN, THROMBOXANE, AND LEUKOTRIENE RESEARCH vol. 21A , 1990 pages 109 - 111 J. A. SALMON 'Inhibition of 5-lipoxygenase: development of hydroxamic acids and hydroxyureas as potential therapeutic agents' see page 110, paragraph 2-4, page 111, first paragraph -----	1-12

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/GB94/00886

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 6,7
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 6 and 7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

.rmation on patent family members

Intern al Application No
PCT/GB 94/00886

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0196184	01-10-86	AU-B-	602485	18-10-90
		DE-A-	3686733	22-10-92
		JP-A-	61257951	15-11-86
		US-A-	4738986	19-04-88
		US-A-	4977188	11-12-90
EP-A-0351214	17-01-90	JP-A-	2088553	28-03-90